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Obstructive Sleep Apnoea And Retinopathy in Patients With Type 2 Diabetes: A Longitudinal Study

Quratul A Altaf*[1,2], Paul Dodson*[2,3,4], Asad Ali[5], Neil T Raymond[6], Helen Wharton[2,3], Hannah Fellows[2,3], Rachel Hampshire-Bancroft[2,3], Mirriam Shah[2,3], Emma Shepherd[2,3], Jamili Miah[2,3], Anthony H Barnett[1,2], Abd A Tahrani[1,2]

[1]Centre of Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK.

[2]Department of Diabetes and Endocrinology, Heart of England NHS Foundation Trust, Birmingham, UK

[3]Heart of England Retinal Screening Centre, Heart of England NHS Foundation Trust, Birmingham, UK

[4]School of Life and Health Sciences, Aston University, Birmingham, UK

[5]Department of Respiratory Medicine, University Hospital of Coventry and Warwickshire, Coventry UK

[6]Independent Epidemiology and Statistical Consultant, Epidemiology, Research Design and Statistical Consulting (ERDASC), Leicestershire, UK

*Joint first authors

Corresponding author:

Dr. Abd A Tahrani, Centre of Endocrinology, Diabetes and metabolism, School of Clinical and experimental medicine, Birmingham B15 2TT, UK a.a.tahrani@bham.ac.uk; Tel: +44-7801549960

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At Glance Summary

Obstructive sleep apnoea is known to be common in patients with type 2 diabetes. Previous studies showed a cross-sectional association between OSA and diabetes-related microvascular complications (such as nephropathy and neuropathy). There are no published studies assessing the relationship between OSA and diabetic retinopathy longitudinally. Our study is the first to prospectively examine the impact of OSA on diabetic retinopathy. Our study showed that obstructive sleep apnoea was independently associated with maculopathy and sight threatening retinopathy in patients with Type 2 Diabetes and that OSA is associated with the development of advanced (pre-proliferative and proliferative) retinopathy longitudinally over approximately 4 years period in patients with Type 2 diabetes.

Abstract

Aims: To assess the relationship between obstructive sleep apnoea (OSA) and diabetic retinopathy (DR) in patients with type 2 diabetes (T2D) and to assess whether OSA is associated with its progression).

Methods: A longitudinal study from diabetes clinics in two UK hospitals was conducted. Patients known to have any respiratory disorder (including OSA) were excluded. DR was assessed using 2x45degrees retinal images per eye. OSA was assessed using a home-based, multi-channel cardiorespiratory device.

Results: 230 patients were included. Sight threatening DR (STDR) and OSA prevalence was 36.1% and 63.9% respectively. STDR prevalence was higher in patients with OSA (OSA+) vs. those without (OSA-) (42.9% vs. 24.1% (p0.004). After adjustment for confounders, OSA remained independently associated with STDR (OR 2.3, 95%CI 1.1-4.9, p=0.04).

After a median (IQR)follow-up of 43.0 (37.0-51.0) months, OSA+ patients were more likely to develop pre-/proliferative DR compared to OSA- patients (18.4% vs. 6.1%, p=0.02). After adjustment for confounders, OSA remained an independent predictor of progression to pre-/proliferative DR (OR 5.2, 95%CI 1.2-23.0, p=0.03). Patients who received continuous positive airway pressure (CPAP) treatment were significantly less likely to develop pre-/proliferative DR.

Conclusions: OSA is associated with STDR in patients with T2D. OSA is an independent predictor for the progression to pre-/proliferative DR. CPAP treatment was associated with reduction in pre-/proliferative DR. Interventional studies are needed to assess the impact of OSA treatment on STDR.

Abstract word count: 226

Key words: obstructive sleep apnoea, diabetic retinopathy, maculopathy

Introduction

Diabetic retinopathy (DR), affects 40-50% of patients with diabetes and is a leading cause of blindness in the Western world and results in significant morbidity and economic burden.[1;2]Important risk factors include age, poor glycaemic control , hypertension, diabetes duration, dyslipidaemia and genetic factors.[1;3]Although the precise aetiology of DR remains debated, increased inflammation, oxidative stress, and activation of multiple pathways, are thought to result in functional and/or structural defects involving the microvasculature. These will increase vascular permeability (which can lead to macular oedema) or cause ischaemia leading to increased vascular endothelial growth factor (VEGF) and neovascularisation.[1;4]Despite improvements in the control of metabolic and vascular risk factors, DR remains very common.[5]and a significant proportion of DR progresses to sight-threatening diabetic retinopathy (STDR)[1]. Hence, improved understanding of the pathogenesis of DR is important in order to identify new treatment targets/strategies.

Obstructive sleep apnoea (OSA) is very common in patients with type 2 diabetes (T2D).[6-10]. We have previously reported that OSA is associated with peripheral neuropathy, nephropathy and estimated glomerular filtration (eGFR) decline in patients with T2D independently of obesity.[10;11]We have also shown that OSA is independently associated with increased nitrosative and oxidative stress and impaired microvascular regulation in patients with T2D[10].T2D is also a risk factor for severe nocturnal hypoxaemia.[12] Hence, it seems reasonable to speculate that OSA could play a role in the pathogenesis STDR particularly since OSA is also associated with many of the pathophysiological deficits found in DR (including inflammation, oxidative stress and increased VEGF).[13-18]

The aim of this study was therefore to determine the interrelationships of OSA and STDR in subjects with T2D and assess whether OSA is associated with DR progression. Some of the findings of this paper were presented in the form of abstracts.[19]

Methods:

We conducted an observational cross-sectional study which was converted to a longitudinal prospective study in subjects with T2D. Patients with respiratory disease (including pre-diagnosed OSA), end-stage renal disease or non-diabetic retinopathy were excluded (**Figure 1**). Patients were recruited consecutively from the out-patient diabetes departments of two secondary care hospitals in the UK (Birmingham Heartlands Hospital and Royal Stoke University Hospital). The project was approved by the Warwickshire Research Ethics Committee (REC number 08/H1211/145), and all patients provided written informed consent.

OSA was assessed by a single overnight home-based cardio-respiratory study using a portable multi-channel device (Alice PDX, Philips Respironics). Sleep studies were scored in accordance with the American Academy of Sleep Medicine (AASM) guidelines using the hypopnea definition of ≥ 4% oxygen desaturation and ≥ 30% reduction in nasal air flow signal.[20] Sleep studies of <4 hours of adequate recordings were repeated and if the quality remained poor they were excluded from analysis. All sleep studies were double scored manually and further scoring was performed in cases of discrepancy (by a consultant in sleep medicine, AA). An apnoea hypopnea index (AHI) ≥ 5 events/hour was consistent with OSA diagnosis.[21] OSA severity was assessed based on the AHI and the oxygen desaturation index (ODI) based on 4% oxygen desaturation. OSA was classified into mild, moderate and severe based on AHI ≥ 5 - < 15, 15 - < 30 and ≥ 30 events/h respectively. Data regarding continuous positive airway pressure (CPAP) treatment was collected as part of routine care as all patients with moderate to severe OSA at baseline were referred to the sleep clinic in the respective NHS trusts for further assessment and decisions regarding treatment. CPAP was offered to all patients with moderate to severe OSA. CPAP usage data were obtained from the electronic patients record approximately 2.5 years following the OSA diagnosis and referral to the sleep clinic. CPAP usage > 4 hours/night on 70% of days was considered to indicate compliance.[22]

DR/STDR was assessed using 2x45 degrees digital retinal images per eye as per the English National Screening programme guidelines (Table 1).[23] The retinal images included in this study were obtained during routine care as patients with diabetes in England are invited to have retinal images as part of

the national screening program once a year. All retinal images were graded at least twice with further grading performed in cases of discrepancy by a consultant ophthalmologist. Patients with ungradable images were examined by a consultant ophthalmologist. STDR was defined as the presence of pre-proliferative or proliferative DR, maculopathy or photocoagulation (Table 1).[23] Advanced DR was defined as having pre-proliferative (R2) or proliferative (R3) DR.

The cross-sectional baseline recruitment analysis designed to explore the relationship between OSA and STDR was conducted using data collected between 2009 and 2010. In order to explore the impact of OSA on the rate of progression of STDR, a longitudinal analysis using retinal images from one of the study centres was performed in 2014. All patients who had at least one retinal screening following the baseline visit were included in the longitudinal analysis. All images between baseline and end of follow-up were reviewed and the worst retinal grades prior to receiving DR treatment were included in the analysis. Progression to maculopathy was assessed by examining the progression from no maculopathy (M0) to maculopathy (M1) after excluding patients with M1 at baseline. Progression to advanced DR was examined by assessing the progression from no (R0) or background (R1) DR to pre-proliferative (R2) or proliferative (R3) DR after excluding patients who had R2 or R3 at baseline. In analysing retinal imaging grading, the worst eye grade was used.

Sleep study scorers were blinded to patient's DR grade and retinal graders were blinded to the patient's OSA status. All data (apart from the retinal images) were obtained during one-to-one interview.

Data analysis was performed using SPSS 22.0 software (SPSS Inc, Chicago, USA). Data are presented as mean (SD) or median (IQR) depending on data distribution. Independent continuous variables were compared using the Student's t-test or the Mann-Whitney test. Categorical variables were compared using the Chi-squared test. Correlations between continuous variables were performed using the Pearson or Spearman tests. All statistical tests conditions/assumptions were adhered to throughout the analysis.

To assess whether OSA and/or hypoxaemia measures are independently associated with STDR, Advanced DR and maculopathy, multiple logistic regression (forced entry method) was used, in

which STDR, advanced DR and maculopathy status were the outcome measures respectively and OSA and other possible confounders were the covariates.

To assess the predictors of DR progression, multiple logistic regression was used with progression to maculopathy and progression to advanced DR as the outcomes and OSA and other confounders as the covariates (please see the results for a full list of the covariates).

To assess the relationship between OSA severity and the outcome measures in the cross sectional and longitudinal analysis, tertiles of AHI and ODI were used in the logistic regression models.

Collinearity was considered in assessing fit of models to data. Based on the tolerance and the VIF tests there was no evidence of collinearity. However, based on the condition index there was evidence of collinearity with condition index value > 30 but there was no variance proportions > 0.5. Sequentially removing variables involved in multicollinearity had limited impact on models estimates for the main exposure. Hence, final models presented included variables based on the known outcome-related risk factors and/or possible confounders and/or variables that differed between patients with and without OSA, regardless of the presence of collinearity. A p value < 0.05 was considered significant.

Results:

Two hundred and sixty-six patients were recruited, 36 were excluded, leaving 230 patients for baseline analysis (**Figure 1**). Of these 230 patients, 57.0% (n=131) were men and 54.8% (n=126) White Europeans and 45.2% (n=104) South Asians. There were no differences between those who were included and those excluded in regards to the prevalence of DR, maculopathy or STDR.

OSA prevalence was 63.9% (n=147). The prevalence of mild, moderate and severe OSA were 37.8% (n=87), 14.8% (n=34) and 11.3% (n=26) respectively. STDR prevalence was 36.1 % (n=83), DR prevalence was 63.5% (n=146) (R0 36.5% (n=84), R1 48.3% (n=111), R2 6.5% (n= 15), R3 8.7% (n= 20)). Prevalence of advanced DR was 15.2% (35) and maculopathy prevalence was 31.7% (n=73).

The prevalence of OSA was higher in White Europeans. Patients with OSA (OSA+) were older, more obese and had higher systolic BP compared to those without OSA (OSA-) (**Table 2**). The use of antihypertensive agents and insulin was higher in OSA+ patients, whilst there were no differences in the use of anti-platelet or lipid-lowering therapy (**Table 2**).

Cross-sectional analysis

The prevalence of STDR, advanced DR (R2 or R3) and maculopathy were significantly higher in OSA+ patients compared to those without OSA (**Table 3**).

OSA and DR; the multivariable analysis

To assess whether the relationship between OSA and STDR is secondary to or independent of possible confounders, logistic regression models were used (**Table 4**). Despite adjustment, OSA remained independently associated with STDR (**Table 4**). In addition to OSA (OR 2.3, 95%CI 1.1-4.8, p=0.03); diabetes duration (OR 1.1, 95%CI 1.0-1.1, p=<0.001), and HbA1c (OR 1.3, 95%CI 1.0-1.7, p=0.01) were also independently associated with STDR.

OSA was also independently associated with maculopathy (OR 2.6, 95%CI 1.2-5.8, p=0.01) (**Table 4)**.

For the relationship between OSA severity and DR please see online supplement.

OSA and DR progression: Longitudinal analysis

We hypothesise that retinopathy progression from background to more advanced stages is accelerated by the presence of OSA. Therefore, in order to explore this construct, a longitudinal analysis was conducted in 199 patients out of 230 patients as follow up data was available from one site only. The average follow up was 43.0 (37.0-51.0)months. There was no significant difference in the median (IQR) follow up duration between patients without (n=71) and with OSA (n=122) (45.0 (37.0-51.0) months vs. 42.5 (36.0-51.0) months respectively, p=0.32). A summary of follow-up duration and DR progression in patients with R0 at baseline in patients with and without OSA can be found in Figure 1 of the online supplement.

Examining the progression from R0 or R1 to advanced DR (R2 or R3), 164 cases were available for analysis (out of 199) after excluding 29 patients who had advanced DR at baseline and 6 cases of loss of follow-up. Out of the 164 patients included in this analysis 66 (40.2%), 60 (36.6%), 19 (11.6%) and 19 (11.6%) had no, mild, moderate and severe OSA respectively. For the baseline characteristics of this population please refer to the online supplement. The proportion of patients progressing to advanced DR was higher in OSA+ patients (18.4% (n=18) vs. 6.1% (n=4), p=0.02 for OSA+ and OSA- respectively), with similar trends in South Asians (14.0% (n=6) vs. 8.9% (n=4), p=0.45) and White Europeans (21.8% (n=12) vs. 0.0% (n=0), p=0.02).

Data from 129 (out of 199) subjects were available to examine the progression to maculopathy (M0 to M1) after excluding 65 patients with M1 at baseline and 5 cases of loss of follow-up. There was no significant difference in maculopathy progression between OSA+ and OSA- patients (20.8% (n=15) vs. 19.3% (n=11), p=0.83 for OSA+ and OSA- respectively).

Similarly, data from 121 patients (out of 199) was available to examine the progression to STDR after excluding 74 patients with STDR at baseline and 4 cases of loss of follow-up. The proportion of patients progressing to sight threatening DR was not statistically different between OSA+ and OSA- patients (20.6% (n=14) vs. 13.2% (n=7), p=0.29 for OSA+ and OSA- respectively) regardless of ethnicity (South Asians: 21.2% (n=7) vs. 19.4% (n=7), p=0.86); White Europeans: 20.0% (n=7) vs. 0.0% (n=0), p=0.05).

After adjustment for ethnicity, gender, diabetes duration, age at diabetes diagnosis, systolic blood pressure, HbA1c, eGFR, BMI, oral anti-hyperglycaemic agents and insulin use and number of anti-hypertensive medications (Nagelkerke R^2 for the model 0.42), OSA remained an independent predictor of progression to advanced DR (OR 5.2, 95%CI 1.2-23.0, p=0.03) (**Table 5**). There was also a dose-effect relationship showing that moderate to severe OSA (vs. no OSA), and tertiles 3 (vs. tertile 1) of AHI and ODI were significantly associated with progression to advanced DR (**Table 5**).

In order to assess whether differences in follow up might account for the observed relationship between OSA and progression to advanced DR, we compared the follow-up duration in patients with OSA who progressed and did not progress to advanced DR. We calculated the follow-up based on two methods: 1. using the latest available retinal image or clinical data when the data was accessed in 2014 as detailed in the methods; 2. Using first mention of progression to advanced DR in electronic records or the retinal screening images. The median (IQR) follow-up (based on first mention of advanced DR in the records) in patients with OSA who did not progress (n=80) vs. those who progressed (n=18) to advanced DR was 44.0 (37.0-51.0) months vs. 32.5 (21.8-42.3) months respectively (p=0.006). This data suggest that the follow-up duration was significantly shorter in patients with OSA who developed advanced DR compared to those who did not develop advanced DR. Compared the follow-up duration (based on the date of the last available record in 2104), we found no difference between patients with OSA who did not progress and those who progressed to advanced DR 44.0 (37.0-51.0) months vs. 43.5 (35.5-52.5) months respectively (p=0.9). This data suggest that our findings are not related to a longer follow-up in patients who had OSA and progressed to advanced DR. In addition, adding the follow-up duration (based on the date of last available record in 2014) to the regression model did not change our findings (The Nagelkerke R^2 remained 0.42; OR for progression to advanced DR in patients with OSA vs. those without OSA was 5.2 (95%CI 1.2-23.0, p= 0.03)). Adding the follow-up duration (based on the first mention of advanced DR in the records) did not change the results either (Nagelkerke R^2 0.5; OR 5.4, 95%CI 1.1-27.4, p=0.04). Hence, the length of follow-up does explain the associations between OSA and progression to advanced DR in our study.

We also assessed the impact of changes in HbA1c during the follow-up on the association between OSA and progression to advanced DR; we found that these associations are independent of changes in HbA1c during the follow-up. More details are included in the online supplement

CPAP and DR progression

CPAP lowered the progression to advanced DR and maculopathy, but this was statistically significant only in the progression to advanced DR category (please see online supplement for details)

Discussion:

This is the first report to examine the relationship between OSA and DR longitudinally. T2D and OSA frequently co-exist and can be associated with a range of metabolic and physiological perturbations which have also been implicated in the pathogenesis of DR. Our study demonstrates that OSA (even when mild) is independently associated with STDR, maculopathy and advanced DR in patients with T2D. We have also shown that OSA is an independent predictor of progression to R2 or R3 over approximately 4 years period and that CPAP treatment might have a beneficial impact on DR progression.

The population in our report comprises subjects attending large inner city, hospital-based diabetes clinics in which the known duration of diabetes was approximately 10 years. Many of the subjects already exhibited established diabetes complications (such as albuminuria as indicated in **Table 2**).The participant characteristics are similar to those reported previously from a different region in the UK,[24] suggesting that the current study sample was representative of the wider T2D population in secondary care. However, whether our findings are applicable to patients typically managed in primary care and those with a shorter duration of diabetes remains to be examined. The high prevalence of OSA in our sample is consistent with other studies in subjects with T2D.[6-9] The prevalence of STDR in our cohort (36.1%) is higher than that reported in the literature (5-15%),[1;25]reflecting differences in the cohorts and DR risk factors in the various studies.

OSA+ patients differed from those without OSA in regards to multiple demographic and metabolic factors. Nevertheless, the association between OSA and advanced DR remained independent despite adjustment for these confounders. STDR, and maculopathy were also associated with mild OSA. This

suggests that the adverse impact of OSA in patients with T2D occurs even in patients with mild degrees of OSA and it is possible that the impact of mild OSA is magnified in tissue that is already predisposed to damage because of chronic hyperglycaemia. This is further exacerbated by the increased retinal oxygen requirements during night adaptation; hence, even mild hypoxia can result in major adverse consequences to the retina.[26] In addition, there was a dose-response relationship in the association between OSA and progression to advanced DR as this association was statistically significant mainly in patients with moderate to severe OSA and in patients with highest AHI and ODI tertiles, suggesting potentially that OSA exacerbated retinal ischaemia which is an integral part of the development of pre-proliferative and proliferative DR.

There are several mechanisms that can link OSA to maculopathy and pre-proliferative and proliferative DR. Retinal ischemia in diabetes result in the stimulation of hypoxia-inducible factors (HIFs) , which are transcriptional factors that are activated under hypoxic conditions resulting in the expression of multiple gene products, including VEGF[27]. Increased VEGF leads to the development of proliferative DR; and retinal ischaemia is the main stimulant of VEGF secretion resulting in proliferative retinopathy; and as a result anti-VEGF are currently used in clinical practice to treat DR.[1;4] The hypoxaemia associated with OSA has been shown to be associated with increased VEGF, which was lowered by CPAP treatment.[28] This is particularly important as the retina is particularly prone to hypoxic damage during night hours[29], which is the same time in which OSA associated hypoxaemia occurs. In addition, endothelial dysfunction plays an important role in the development of DR and manculopathy; we and others have previously shown that OSA (and its associated cyclical oxygen desaturations and disruption in sleep architecture) can lead to the activation of PARP, PKC, and the polyol pathway, and increased AGE production, inflammation and oxidative and nitrosative stress, all of which can lead to endothelial dysfunction and can contribute to the observed associations between OSA and DR in our study.[10;30;31 10].

In our study, the observed cross-sectional and longitudinal associations between OSA and DR were much stronger in White Europeans compare to South Asians. There might be several plausible reasons for the observed ethnic differences. South Asians with T2D are known to be at an increased risk of DR and STDR compared to White Europeans with T2D.[32] Hence, in South Asians there are factors other than OSA that result in increased risk of DR in this population compared to White Europeans making the impact of OSA on DR in South Asians smaller and hence requiring significantly larger sample size to detect. This is supported by our analysis showing that the direction of the relationship between OSA and STDR, advanced DR, and maculopathy cross-sectionally and longitudinally is similar between South Asians and White Europeans, but the magnitude is greater in White Europeans. Another important factor is that we have shown in this cohort previously that OSA is less common and less severe in South Asians compared to White Europeans with T2D;[33] which might also contribute to the weaker relationship between OSA and STDR, maculopathy and advanced DR observed in this study in South Asians compared to White Europeans.

Two previous studies have shown an association between OSA and DR, but there are important differences between these studies and ours. These studies were cross-sectional and, unlike ours, a longitudinal analysis was not performed. Additionally, the previous studies included highly selected populations such as Japanese patients who underwent vitreous surgery[34] or only White European men;[35] Our study was more comprehensive and included patients regardless of their ethnicity, gender or severity of retinopathy. Moreover, in prior reports the diagnosis of DR was based on case records rather than using retinal images as utilized in our study.[34] OSA assessment also differed between the studies; one study used pulse oximetry to diagnose OSA,[34]whilst the other used a complex multi-step approach based on questionnaires followed by pulse oximetry on a selected subgroup.[35] We performed a more in depth assessment using a multi-channel device in all the study participants. Critically, the previous studies did not adjust for important possible confounders such as blood pressure, BMI, medication use, or used suboptimal measures, such as self-reported

BMI.[34;35] In contrast, our extensive data ascertainment allowed us to adjust for a wide range of possible confounders.

Although OSA has been associated with several other ocular pathologies in patients without diabetes; [36-40] changes similar to DR have not been described in patients with OSA without diabetes suggesting that the presence of hyperglycaemia is mainly responsible for the development of DR but OSA might contribute to the progression of the disease. This is supported by our data showing that the higher prevalence of DR in patients with OSA vs. those without OSA in our study was mainly driven by a higher prevalence of advanced DR but the prevalence of background DR (or early DR) was similar in patients with and without OSA; suggesting that OSA contribute to the progression rather than the development of the disease. This is biologically plausible, particularly since the intermittent hypoxia associated with OSA can result in retinal ischemia and increased VEGF production resulting in the development of advanced DR. The lack of OSA effect on maculopathy development longitudinally could be due to differences in the pathogenesis between maculopathy and pre-/proliferative DR or due to the methods used to diagnose maculopathy in this study (i.e. images) rather than the actual measurement of macular thickness using ocular coherence tomography.

Assessing the impact of CPAP treatment on DR and DR progression was not the focus of this study. The available observational data, however, suggest that CPAP-compliance might have a favourable impact on DR progression although these patients had worse AHI. The progression to maculopathy in the CPAP-compliant group was lower than that in non-compliant group and similar to patients with mild OSA. However, it is difficult to assess CPAP efficacy from observational data due to the small numbers of patients who were compliant. Nonetheless, these data provide further justification for future research to assess the impact of CPAP on the development and progression of DR, and highlight the challenges of CPAP compliance in patient with T2D.

Our study has several limitations. We have used home-based portable multi-channel respiratory devices rather than in-patient overnight polysomnography. However, this approach is well established.[41;42] Our sample population is also drawn from hospital-based diabetes centres-,hence we cannot necessarily extend our conclusions to other patient populations. We have used 2-field images to assess DR, rather than 7-field images, which might result in missing peripheral retinal lesions. This is unlikely to affect the results unless patients with OSA are more likely develop more peripheral lesions compared to patients without OSA (or vice versa), but there is no evidence to support this. The limited number of events over the follow-up period did not allow us to perform more in depth analysis about the relationship between OSA and DR progression.

In conclusion, we have identified a relationship between OSA and STDR and maculopathy in patients with T2D. OSA was also an independent predictor for the development of advanced DR. There was a dose-response relationship between OSA severity and the development of Advanced DR. CPAP-compliance was associated with reduction in the development of advanced DR. Interventional studies are needed to assess the impact of OSA treatment on the development of advanced DR.

Conflict of interest:

None

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Figure 1: The study flow diagram. *Represents numbers after excluding patients with the condition at baseline in order to assess progression. DR: Diabetic Retinopathy; STDR: Sight Threatening DR

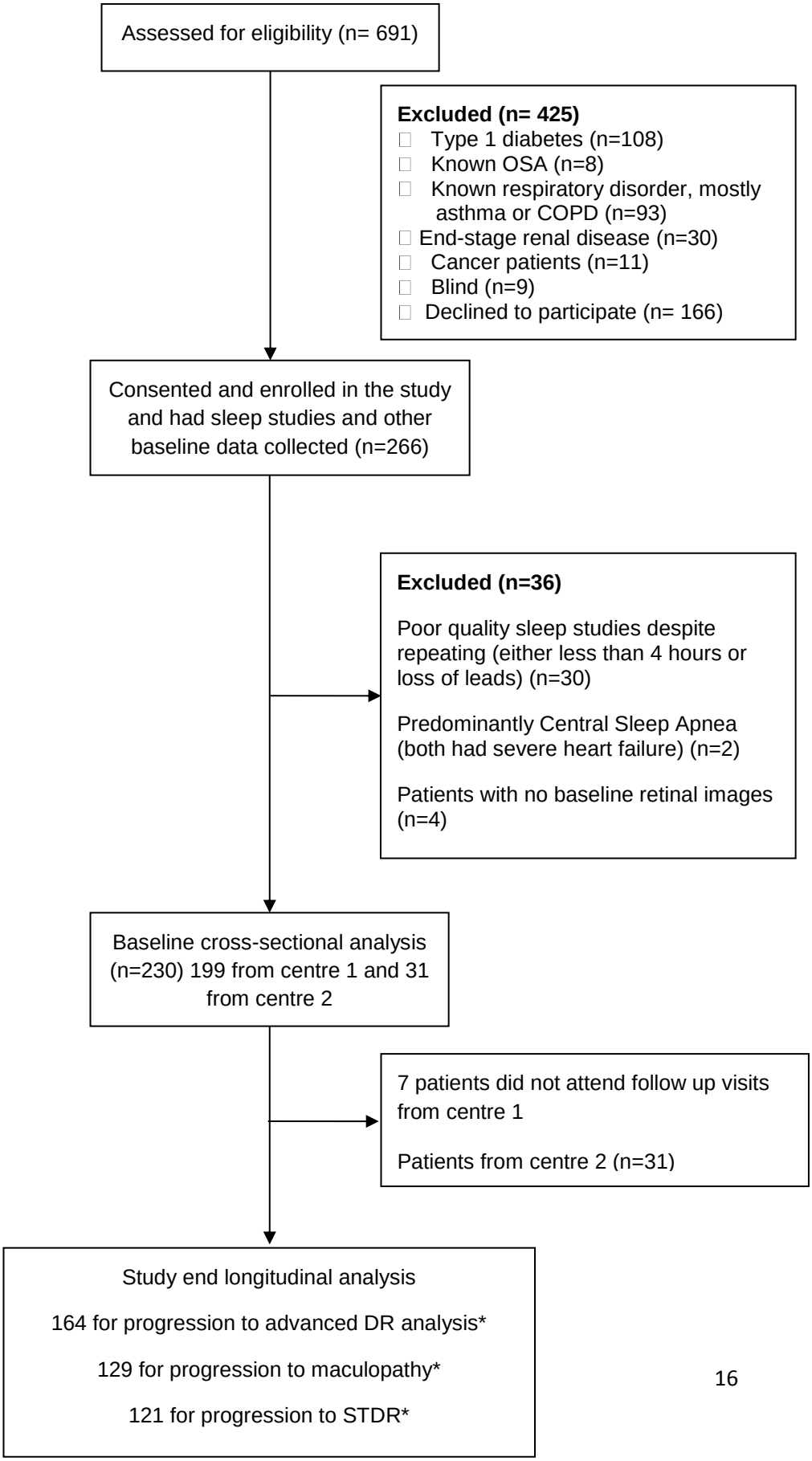

Table 1: Disease grading protocol in National Guidelines on Screening for Diabetic Retinopathy.

Retinopathy (R)		
Level 0	None (R0)	
Level 1	Background (R1)	Microaneurysm(s)
		Retinal haemorrhage(s) ± any exudate
Level 2	Pre-proliferative (R2)	Venous beading
		Venous loop or reduplication
		Intraretinal microvascular abnormality (IRMA)
		Multiple deep, round or blot haemorrhages
		(CWS—careful search for above features)
Level 3	Proliferative (R3)	New vessels on disc
		New vessels elsewhere
		Preretinal or vitreous haemorrhage
		Preretinal fibrosis ± tractional retinal detachment
Maculopathy (M)		
Level 0	M0	
Level 1	M1	Exudate within 1 disc diameter (DD) of the centre of the fovea
		Circinate or group of exudates within the macula
		Retinal thickening within 1 DD of the centre of the fovea (if stereo available)
		Any microaneurysm or haemorrhage within 1 DD of the centre of the fovea only if associated with a best VA of ≤ (if no stereo) 6/12
Photocoagulation (P)	(P1)	Focal/grid to macula

Table 2: Participant characteristics in relation to OSA status. Data presented mean (SD) or % (n). GFR: Glomerular Filtration Rate. Analysis performed using the Chi-square test for categorical variables, the independent t test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

	OSA- (n=83)	OSA+ (n=147)	P value
Male	41.0% (34)	66.0% (97)	<0.001
White European	38.6% (32)	63.9% (94)	<0.001
Age (years)	54.7 (11.9)	58.7 (11.4)	0.01
Diabetes duration (years)	10.7 (7.23)	13.1 (7.8)	0.02
Body Mass Index (kg/m^2)	31.7 (7.0)	35.8 (8.7)	<0.001
Waist circumference (cm)	107.1 (15.8)	117.2 (15.9)	<0.001
Systolic blood pressure (mmHg)	125.7 (15.6)	132.6 (17.4)	0.003
Diastolic blood pressure (mmHg)	77.2 (10.2)	78.3 (10.0)	0.4
HbA1c (%)	8.1 (1.5)	8.3 (1.3)	0.06
Total cholesterol (mmol/L)	4.0 (1.1)	3.9 (1.0)	0.54
Triglycerides (mmol/L)	1.8 (1.2)	2.1 (1.3)	0.04
Estimated GFR (ml/min/1.73 m^2)	93.1 (24.7)	82.7 (27.4)	0.008
Epworth sleepiness score	6.8 (5.7)	9.1 (5.6)	0.004
Smoking (current or ex-smoker)	38.6% (32)	40.8% (60)	0.74
Alcohol (consumes alcohol)	14.5% (12)	34.7% (51)	0.001
Oral hypoglycaemic agents	97.6% (81)	90.5% (133)	0.04
Thiazolidinediones	14.5% (12)	15.0% (22)	0.92
Insulin	41.0% (34)	59.9% (88)	0.006
GLP-1 analogue	7.2% (6)	13.6% (20)	0.14
Anti-hypertensive agents	73.5% (61)	85.7% (126)	0.02
Lipid lowering therapy	85.5% (71)	83.7% (123)	0.71
Fibrates	4.8% (4)	4.8% (7)	0.9
Anti-platelet agents	60.2% (50)	71.4% (105)	0.08
Ischemic heart disease	16.9% (14)	21.8% (32)	0.37
Diabetic nephropathy	23.8% (19)	50.7% (71)	0.005

Table 3: The relationship between OSA status and sight threatening diabetic retinopathy, retinopathy and maculopathy (unadjusted analysis). Data presented as % (n) of the respective OSA category.

Total cohort		**OSA- (n=83)**	**OSA+ (n=147)**	**P values**
Sight threatening diabetic retinopathy*		24.1% (20)	42.9% (63)	0.004
Advanced retinopathy		7.2% (6)	19.7% (29)	0.01
Retinopathy	R0	45.8% (38)	31.3% (46)	0.03
	R1	47% (39)	49% (72)	
	R2	2.4% (2)	8.8% (13)	
	R3	4.8% (4)	10.9% (16)	
Maculopathy		19.3% (16)	38.8% (57)	0.002
South Asians		**OSA- (n=51)**	**OSA+ (n=53)**	
Sight threatening diabetic retinopathy*		27.5% (14)	35.8% (19)	0.36
Advanced retinopathy		9.8% (5)	15.1% (8)	0.42
Retinopathy	R0	39.2% (20)	26.4% (14)	0.52
	R1	51.0% (26)	58.5% (31)	
	R2	3.9% (2)	7.5% (4)	
	R3	5.9% (3)	7.5% (4)	
Maculopathy		21.6% (11)	34% (18)	0.16
White Europeans		**OSA- (n=32)**	**OSA+ (n=94)**	
Sight threatening diabetic retinopathy*		18.8% (6)	46.8% (44)	0.005
Advanced retinopathy		3.1% (1)	22.3% (21)	0.01
Retinopathy	R0	56.3% (18)	34.0% (32)	0.04
	R1	40.6% (13)	43.6% (41)	
	R2	0.0% (0)	9.6% (9)	
	R3	3.1% (1)	12.8% (12)	
Maculopathy		15.6% (5)	41.5% (39)	0.01

*****pre-proliferative or proliferative retinopathy, maculopathy or laser treatment

Table 4: Assessing the association between OSA and STDR, maculopathy and advanced diabetic retinopathy (DR) (R2 or R3) based on the baseline cross-sectional analysis using logistic regression models (forced entry method). The odds ratios (OR) reported are the odds for having the outcome of interest (STDR, Maculopathy or advanced DR depending on the model) in OSA+ compared to OSA- patients. Model 1 is adjusted for OSA, ethnicity, age at diabetes diagnosis, diabetes duration, gender, HbA1c, BMI, systolic blood pressure, insulin use, number of anti-hypertensive agents, oral anti-hyperglycaemic agents and eGFR. Replacing BMI with waist circumference or waist/hip ratio does not change the results significantly. Inserting BMI and waist circumference together into the model did not have an impact on the OR.

Model	Nagelkerke R Square for the model	Odds ratio	95% confidence interval	P value
Sight Threatening Diabetic Retinopathy*				
Unadjusted: OSA	0.05	2.3	1.3-4.3	0.005
Model 1	0.32	2.3	1.1-4.9	0.04
Maculopathy				
Unadjusted: OSA	0.05	2.6	1.4-5.0	0.003
Model 1	0.28	2.7	1.2-5.9	0.01
Advanced DR (R2 or R3)				
Unadjusted: OSA	0.05	3.1	1.3-8.0	0.02
Model 1	0.32	3.0	1.0-9.3	0.06

*pre-proliferative or proliferative retinopathy, maculopathy or laser treatment)

Table 5: The longitudinal impact of OSA on progression to advanced DR (R2 or R3) over the follow up period. The odds ratios (OR) reported are the odds for progressing to advanced DR in OSA+ compared to OSA- patients and in AHI tertiles 2 and 3 compared to AHI tertile 1 and in ODI tertiles 2 and 3 compared to tertile 1. The model is adjusted for ethnicity, gender, diabetes duration, age at diabetes diagnosis, systolic blood pressure, HbA1c, eGFR, BMI, oral anti-hyperglycaemic agents and insulin use and number of anti-hypertensive medications. OSA status (yes/no), OSA status (no, mild, moderate to severe), AHI tertiles and ODI tertiles were inserted into the model separately. The AHI tertiles were < 4.8 events/hour, 4.8-11.89 events/hour and ≥ 11.90 events/hour for tertiles 1,2 and 3 respectively. The ODI tertiles were < 4.1 events/hour, ODI 4.1-11.39 events/hour and ≥ 11.40 events/hour for ODI tertiles 1,2 and 3 respectively. Nagelkerke R^2 for all the 3 models in this table was 0.42

	OR	95% CI	P value
OSA (vs. no OSA)	5.2	1.2-23.0	0.03
Mild OSA (vs. no OSA)	3.7	0.7-18.0	0.11
Moderate to severe OSA (vs. no OSA)	14.8	2.3-94.7	0.005
AHI tertile 2 (vs. tertile 1)	4.0	0.8-19.8	0.09
AHI tertile 3 (vs. tertile 1)	7.5	1.4-41.3	0.02
ODI tertile 2 (vs. tertile 1)	3.9	0.8-18.8	0.09
ODI tertile 3 (vs. tertile 1)	6.0	1.2--31.6	0.03

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